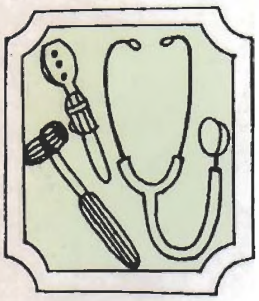

The Internist

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Chiropractic Manipulative Therapy in the HIV+ Patient

by Brian A. Smith, DC

ABSTRACT

There is increasing evidence demonstrating nervous system control of immune responses. Neuropeptides act directly and indirectly on the immune system. Immunomodulatory substances have measurable effects on the central nervous system. Lymphocytes are able to produce and release a variety of substances once thought to be solely under the domain of the nervous system. The complex structure of the vertebral unit allows for multiple sites and mechanisms of possible insult. Aberrant motion of spinal segments have been shown to affect sympathetic nervous system activity. Chiropractic adjustments may affect immunomodulatory neuropeptide levels and T4 lymphocyte counts.

Key Indexing Terms: Immune system, manipulation, chiropractic, HIV, CD4 count, autonomic nervous system.

INTRODUCTION

The Acquired Immune Deficiency Syndrome (AIDS) is characterized by a progressive loss of immune function with specific depletion in the number and function of the helper/inducer T-lymphocytes, known as T-4 or CD-4 lymphocytes coupled with derangement of normal T-8 lymphocyte (cytotoxic or suppresser cell) function (CD represents Cluster Designation).

Drug therapy has been mainly directed toward eradication or inactivation of the presumed cause, the Human Immunodeficiency Virus - 1 (HIV-1) through the use of nucleoside analogues such as AZT, ddI, ddC, 3TC and d4T; non-nucleoside reverse transcriptase inhibitors such as Nevirapine (Viramune), Delavirdine (Rescriptor) and Efavirenz (Sustiva) and the use of protease inhibitors such as saquinavir (Invirase/Fortovase), Ritonavir (Norvir), Indinavir (Crixivan) and Viracept. The nucleoside analogues act by interfering with the function of the viral enzyme reverse transcriptase which is necessary for viral transcription. The protease inhibitors act on the HIV protease which is necessary to cleave viral polyprotein precursors to generate functional proteins in HIV-infected cells.

Within the realm of HIV care it is important to acknowledge the complex relationship between the nervous and immune systems. Anthony Fauci, director of the National Institutes of Allergy and Infectious Disease of the NIH has stated, "Scientists have known for a long time that there are nervous system diseases that are mediated by the immune system. And recently it has become clear that the immune system itself may be regulated by the nervous system. So the immune system has an impact on the nervous system and the nervous system has an impact on the immune system."[1]

DISCUSSION

It has been clearly demonstrated that stimulation of visceral afferent fibers will elicit mass reflex discharges in the corresponding white rami. Natural stimuli to visceral receptors either increase or decrease the discharge rates of sympathetic pre- and post-ganglionic units. It has also been well established that certain classes of neuropeptides act directly and indirectly on immune cells and immune organs. Cytokines are immunomodulating peptides released from white blood cells which have pivotal roles in the coordination of the host defense mechanisms. Interleukin-1 (Il-l) is one such cytokine produced by monocytes, macrophages, lymphocytes, brain and other cells during acute and chronic disease. It participates in the activation and differentiation of lymphocytes. Interleukin-2 (Il-2) is produced by T-lymphocytes and acts in an autocrine manner to initiate proliferation of activated T-cells[2]. Il-1 and Il-2 production and activity are significantly mediated by the autonomic nervous system and interleukin- dependent cellular immune phenomena can also be

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altered by stimulation of the autonomic nervous system[3]. Research has demonstrated eosinophil and neutrophil influx into bronchoalveolar lavage in guinea pigs exposed to aerosolized Substance P and neurokinin A respectively[4]. Tachykinins such as Substance P and neurokinin H enhance 11-2 production by TLymphocytes and stimulates their production[5, 6, 7]. These tachykinins are released in the periphery after antidromic stimulation of afferent sensory c-fibers and can result in neurogenic inflammation[8, 9]. It is known that up to 90% of the Substance P synthesized by c-fibers is transported to the peripheral terminals of the fiber[10]. The immunomodulatory effects of acetylcholine are well known. T-cell activation is enhanced through the "alternative pathway" as demonstrated by a 50% increase in early human E rosette formation after cholinergic drug introduction. B- and T-cell spontaneous or anti-Ig stimulated motility is increased in the presence of carbamycholine (a non-hydrolyzable cholinergic agonist). Cholinergic stimulation accelerates synthesis of antibodies which may reflect direct B-cell stimulation or cooperation between B- and activated T-cells-(ll). Cholinergic stimulation may play a role in thymocyte maturation also[12].

Noradrenergic sympathetic innervation is Most prominent in T-cell areas Of secondary lymphoid organs, spleen, lymph nodes and gut associated organs as well as primary sites of bone marrow and thymus. In the lymph nodes fibers enter via the vasculature, travel through the medullary, cortical and para-cortical regions and branch into the parenchyma, primarily in T-cell and macrophage rich regions. It is theorized that lymphocytes are exposed to norepinephrine by classical neurotransmission throuqh a paracrine mechanism. B-adrenergic stimulation of immune cells causes activation of adenylyl cyclase and elevation of intracellular cyclic AMP[13]. Cyclic AMP levels must be low for lymphocytes to progress to the S-phase in their growth [14].

Neuropeptide Y, cholecystokinin 9, metenkephalin, neurotensin, substance P and calcitonin gene related peptide have demonstrated neuropeptide-like immunoreactivity in neural

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profiles in lymphoid tissue[15, 16, 17, 18]. Loss of normal sympathetic nervous stimulation disrupts the regulation of proliferation and migration of lymphocytes[19]. Sympathectomy decreased CD4+ T-cells in lymph nodes. Alterations in lymphocyte activity does not always correlate with changes in the proportions of T- or B lymphocyte subsets. Sympathetic denervation leads to loss of an important regulatory mechanism in immune system physiology. This is apparently site specific in that both lymph node and spleen T-cell proliferative responses are reduced. In the spleen Il-2 and interferon-(lambda) production is reduced and T-cell proportions are constant. In lymph nodes the reverse occurs, the T-cell proportion is altered while interleukin and interferon levels are unchanged[20]. The intact sympathetic nervous system may function to directly or indirectly affect B-cells as chemical sympathectomy selectively enhances the response to thymus-independent antigens which are known to be influenced by the suppressor (T-8, CD-8) T- lymphocytes[21].

This is not a unidirectional path. It has been demonstrated that immunomodulatory factors such as interleukin-1, histamine, thymic humoral factor and alpha-interferon all alter EEG activity in the area of the brain known to modulate both immune and neuroendocrine secretary activity. Further, it has been shown that lymphocytes can produce and release ACTH, endorphins, enkephalins, vasoactive intestinal peptide and Substance P[22].

Pituitary and/or hypothalamic hormone release is induced by IL-1, Tumor Necrosis Factor (TNF)-alpha and tuftsin. TNF is a factor induced by endotoxin which is characterized by its cytotoxic and/or cytostatic activity on transformed cells and is an essential mediator of the inflammatory response. Tuftsin is a splenic tetrapeptide that activates all functions of phagocytic cells and influences antibody formation as well as inducing Il-1 production. IL-2 will inhibit acetylcholine release from certain areas of the central nervous system[2].

Research concerning chiropractic spinal adjustment and its effect on the sympathetic nervous system is plentiful. There is much literature available on viscerosomatic reflexes[23], somatosympathetic reflexes[24], and nociceptive reflexes[25]. Spinal joint dysfunction has been implicated in sudden cardiac death[26], bowel and bladder dysfunction[27], pulmonary disease[28], coronary artery disease[29], and duodenal ulcer[30].

Structures of concern in the nervous system include the spinal roots and spinal nerves as well as the nerve root sleeve. These structures may be affected by sleeve adhesions, sustained paravertebral muscle contraction through which nerves pass, compressive narrowing of the foramen, constriction at the duroarachnoid junctions of root pouches, and intraforaminal venous congestion due to compression of spinal and radicular veins. Further, axonal excitation and conduction can be affected by hypoxia, pH shifts and other chemical changes due to ischemia. The paravertebral sympathetic ganglia are subject to trauma as well. In the cervical region the major source of trauma is interference from the adjacent muscle groups and the highly mobile nature of the area. The thoracic and lumbar ganglia may be compressed by adhesion to parietal pleura or peritoneum. Compression can block lymphatic drainage in the ganglionic chain with resultant edema of the affected ganglia. Changes in neuronal function from these insults include supernumerary impulses being generated at a deformation site, ephatic transmission at hyperirritable foci, spontaneous generation of action potentials as found in paravertebral sympathetic ganglia under conditions of deformation, edema and other changes in environment; and blocking of axonal transport mechanisms by constriction or compression of axons. Ectopic impulses propagate both orthodromically and antidromically. Dermal sensory nerves stimulated antidromically will have a significant vasodilatory effect on the innervated dermal area with resultant hyperemia[31].

Numerous sensory fibers can be found in sympathetic and parasympathetic nerves. Noxious stimuli from the viscera will excite these autonomic afferent fibers which will stimulate both sympathetic preganglionic neurons in the cord

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and adjacent motor neurons via internuncial transmission. This dual excitation produces, in the former, necessary adaptation to the local environment in the organ and, in the latter, sustained muscular hypertonicity[32]. In this way abnormal somatosympathetic reflexes are created which produce aberrant synaptic connections which will result in a non-functional link between somatic and visceral structures in neurologically related structures. Referred pain and the phenomena of sudomotor and vasomotor, i.e. sympathetic reflexes, of visceral and somatic origin are an example of dysfunctional segmental coupling. The normal adaptive reflexes of the involved organs or structures become disrupted with resultant loss of function[33].

Chiropractic adjustive therapy is designed to address the biomechanical distortions to nerves and related structures that lead to altered excitation and conduction faculties and disturbed trophic function and to restore normal sensory afferent impulses by altering the somatic tissue.

Overstimulation of the sympathetic nervous system, as seen in cases of subluxation, results in increased release of catecholamines. While it is known that loss of catecholamines results in depressed immune function, it is important to remember that they are also inhibitory to T-lymphocytes at high concentrations. In addition, stimulation of Substance P receptors on T-cells by normal levels of Substance P causes increased phagocytosis of yeast particles by polymorphonuclear lymphocytes, increased margination and endothelial adherence of PMN's and monocytes to venules and more degranulation of mast cells causing the release of histamine. Loss of these functions through depressed or elevated sympathetic nervous system activity adversely affects the immune system[34].

Correction of subluxations has been shown to normalize certain sympathetic nervous system responses such as sudomotor and pilomotor activity[33].

Eight patients demonstrating a significant increase in circulating B lymphocytes following four weeks of spinal adjustments was reported in 1980[35].

It has been demonstrated that Substance P levels are increased by 6.4 pg/ml. in test subjects who received high velocity, low amplitude adjustments to the thoracic spine when compared to test subjects receiving sham treatments.

Additionally, PMN's isolated from those receiving adjustments demonstrated statistically significant increases in rates of phagocytosis measured via chemiluminescence. This increased activity may be the result of "priming" by Substance P. Substance P will also induce the release of TNF, Il-I and 11-6[36].

In a pilot study, the effects of specific upper cervical adjustments on the T4 lymphocyte counts of HTV+ subjects were measured over a six month period. The control group, receiving sham adjustments, experienced a 7.96% decrease in total T4 lymphocytes while the group receiving adjustments demonstrated a 48% increase in T4 lymphocyte counts[37]. A larger study is currently underway which will hopefully corroborate the pilot study results. It is very impressive that all of the adjusted subjects demonstrated varying degrees of increased T4 lymphocyte counts over the test period, an unlikely phenomena in a random sampling of HIV+ persons.

To illustrate let us examine lymphadenopathy/ lymphedema of the duodenal lymphatic vessels which open into the pancreaticoduodenal nodes and thence to hepatic and preaortic nodes as might be expected in a patient with an intestinal infection such as cryptosporidium or microsporidium, two of the opportunistic infections encountered in AIDS patients. This will cause sympathetic sensory excitation through the celiac plexus which innervates these lymphatic system components, and thence over the greater and lesser splanchnic nerves. These transmissions enter the spinal canal through spinal roots from the fifth thoracic through the tenth thoracic. Through the aforementioned mechanisms, e.g. ephatic transmission, supernumery impulses, etc., nerve stimulation to any of the organs supplied by these nerve roots: spleen, liver, stomach and pancreas; and to the somatic

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structures innervated by the fifth through tenth thoracic nerve roots, vis-a-vis intercostalis muscles, the internal and external abdominal obliques, the transverse abdominal, the serratus posterior inferior and the rectus abc[ominus muscles and local paravertebral muscle groups including the iliocostalis thoracis, longi-ssimus thoracic, spinalis thoracis, semispinalis thoracis and the multifidi, rotatores and intertransversarii; resulting in abnormal function of the involved organs and muscles. Unbalanced paravertebral muscular contraction is one factor in creating an aberrant motion segment in the spinal column. It has been demonstrated that this subluxated segment causes transmission of abnormal nervous impulses due to several mechanisms including physical deformation of the nerve with resultant ectopic foci, piezoelectrical effect on nerve roots, changes in axonal transport mechanisms and local changes in blood circulation. Restoring normal motion to the affected vertebral unit(s) will decrease, or eliminate, this abnormal nerve transmission, allowing the innervated tissues and organs to function more appropriately.

CONCLUSION

It is clear that the sympathetic nervous system plays an important role in immune function. It has also been demonstrated that proper sympathetic nervous system functioning is, to some extent, dependent on proper musculoskeletal system functioning. We know that both the sympathetic nervous system and musculoskeletal system in HIV+ persons may be deranged. Correction of these derangements should help restore a more normal state of immune function. It has been demonstrated that the chiropractic adjustment is one method of addressing and correcting these derangements.

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